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Foreword

BY JOHN HOLLANDER

WRITING of London's plague-ridden summer of 1592 in his *Summer's Last Will and Testament,* the poet, novelist and pamphleteer Thomas Nashe gave the stanzas of his famous litany a refrain from the English Prayer Book's office for the dead:

Adieu, farewell earth's bliss,
This world uncertain is;
Fond are life's lustful joys,
Death proves them all but toys,
None from his darts can fly,
I am sick, I must die.
Lord, have mercy on us!

Rich men, trust not in wealth,
Gold cannot by you health;
Physic himself must fade,
All things to end are made.
The plague full swift goes by.
I am sick, I must die.
Lord, have mercy on us!

1991 We are now in time of plague. But this time it is during a period of our historical consciousness which would seem to have put the very term "plague," and the realms of ignorance that it signifies for our general knowledge of the etiology of infectious disease, far behind us. The word itself has come to be used in two principle ways. The first designates the epidemic infections by *bacillus pestis* in its various bubonic, pneumonic and septicaemic forms that started to overrun Europe in the fourteenth century, and still manifests for the medical and historial layman an aura of factual rats and lice cloaked by superstitious fiction.

Our other use of "plague" is that of the older and basic term,

the biblical and proverbial one, referring to the ten disasters with which the Lord smote the Egyptians in Exodus. Of these, at most two, the boils and the murrain decimating the livestock —anthrax, hoof-and-mouth, or whatever—were infectious diseases, or in any way like "plague" in the first sense; generally, they comprised a series of graded horrors, from pests through pestilence, through darkness and significantly selective death, which *struck* (and this is the operative word) the Egyptians. For our English word "plague," is derived from the Latin *plaga* which means a blow, a wound, the mark left by something striking one: something with which one has been stricken. It quite rightly translates the Hebrew word for the ten plagues, *maggefot,* which similarly derives from the root *neggef,* or blow. (The word for contagious illness is *dever,* and is used only of one of the plagues, the "pestilence." This is translated by the Latin *pestis,* a word, like infectious disease itself until the nineteenth century, "of obscure origin.") The etymological implication of "plague" privileges the world of the patient, the sufferer, rather than that of the healer, interpreter or understander. A plague is what one has been assaulted with. And when that is some bodily harm seeming to develop from within one, it is rather an *illness* (as the medical anthropologist Arthur Kleinman has distinguished them) than a *disease*—a condition possessed of the sufferer, rather than a conceptual construction of biomedicine.

It is to the Greek historian Thucydides that we owe our canonical analytic account of *pestis,* of "lethal epidemic disease" in the language of this volume's subtitle. His chronicle of the epidemic *(loimos)*—of still disputed biomedical character—that struck the Athenians during the Peloponnesian War is exemplary in its description of the effects of widespread, uncontrollable infectious disease upon the life of the *polis* and, indeed, upon institutions of hope and fear, as in his famous observation that (in Rex Warner's translation) "As for the gods, it seemed to be the same thing whether one worshipped them or

not, when one saw the good and the bad dying indiscriminately." It is also to Thucydides that we owe a notion of the moral consequences of plagues, one reciprocal to that of their moral causes, as in the case of the biblical plagues as God's willed blows of retribution.

Medical science might be said to have come, since the middle of the nineteenth century, to have disinfected the first meaning, that of a specific *pestis,* from contamination by the connotations of *plaga,* the second one. With the very identification of a microbe, together with its vectors of transmission, as the "causes" of the disease, the Divine or otherwise ineffable deliverer—and mode of delivery—of the plague with which one is stricken became a matter of myth and, in its decayed or institutionalized form, catastrophic popular error. We have never been entirely free of the feeling that *pestis* is *plaga.* Any individual person, no matter how rational, is bound to have a private sense of his or her own illness, whatever it may be. More generally, those of us over a certain age can remember when, in the United States, poliomyelitis was still something of an endemic summer plague, spottily dispensed—for all practical purposes—by Fortune. From the point of view of the individual imagination and of the individual illness, cancer, while not communicably infectious, is in its own way epidemic in a plague-like way. All of us feel our illnesses—even those of annoyance, like the common cold—as *plagae,* as blows with which we have been struck. And yet, of course, nobody, and nothing, has delivered them. But for the most part, the concept of *pestis* as *plaga* we have tended to consign to an earlier world-picture or episteme.

It is precisely because of the crucial threat, and the complex social ramifications, of the epidemic spread of the HIV virus in the last decades of the twentieth century that we can feel again how "the plague full swift goes by." But it is generally because of our growing realization that we are no longer able, thanks to three centuries of enlightenment, to feel ourselves delivered

from a specific aspect of how "this would uncertain is," that it has seemed necessary to open up again the book of plague. Our private, personal superstitions and our hopes for being able to dispel them had shifted, it seemed, from the realm of deadly contagious disease to those of perhaps deeper biochemical mysteries. But now we are reminded of such matters as those of personal infectiousness, of rights and responsibilities of the ill and the healthy at a moment in American history when so much vox populi seems to harp on individual rights and entitlements but only on public responsibilities, on how much or how little my neighbor's disease may be, or may be said to be, mine, and so many more. And it is altogether appropriate for us to acknowledge that we have lost a good bit of our conceptual world's certainty, and to proceed to apply to our new confusion some of what, in those same three centuries, we have indeed gained.

Contributors

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Introduction

BY ARIEN MACK

THIS diverse collection of essays represents an attempt to set the recent and alarming outbreak of AIDS in perspective by considering it in the context of the social history of past lethal epidemics. The focus of attention is on the many ways in which diseases, particularly catastrophic infections and contagious diseases, are socially as well as biologically defined. This emphasis is meant to lead to the recognition that diseases are not simple biological entities which belong to the exclusive domain of scientists and physicians. They are social-cultural events as much as biological and medical ones, and so coming to terms with them cannot simply be a matter of waving the scientist's magic wand.

The choice of so ominous and threatening a title as *In Time of Plague* was deliberate and based on at least two reasons. First, for good or ill, the word "plague" effectively captures the emotional associations frequently engendered by reports about AIDS. The word acknowledges the unfamiliar fears it has awakened. After decades of dividing our time between apocalyptic fears of nuclear holocaust and private fears of personal ruin, we now face a threat that is profoundly social, requiring a public, community response. Most of us until recently have assumed, perhaps without thinking, that the number of life-threatening infectious diseases was finite, soon to be cured and prevented by medical science. So the study of plagues was delegated exclusively to medical and social historians. Now it appears that this idea that we stand outside our own history, that we, unlike our forebears, are immune to widespread medical disasters, is very doubtful.

The word "plague" appears in the title for a more specific

reason as well. Its presence points the way to the problem that must be addressed. In fact, the problem we face can be seen in the very considerations that made the word seem appropriate, for the exotic connotations of the term exercise their influence over our emotions, even when the word itself is not spoken. The fact is that the past is both too much and too little with us in our public deliberations about AIDS; its images of disease affect us precisely because we so rarely take them into account. The hope is that these scholarly discussions will allow our present and our past to speak with each other. With luck they may permit us to discern the similarities between our past and our present, untangle overlooked differences, and reflect on how we should now act.

The essays in this book are divided into four sections. The first section, "The Definition and Control of Disease," is concerned with a group of related questions:

(a) How has the definition of disease differed in different historical moments? Are there cultural invariants that determine how diseases are perceived or defined? How does the definition of disease as a consequence of behavior, the presence of some biological process, or as the manifestation of a particular set of symptoms affect the social response?

(b) How have new technologies, advances in the science of epidemiology and mass information gathering changed our perception and response to disease? Under that circumstances has it been deemed appropriate, or is it appropriate, to control information or behavior? For example, when has quarantine been appropriate or effective?

(c) What problems follow from reporting the results of medical research to the public? OR NOT REPORTING

The second section contains only one paper. This paper by Lewis Thomas, "Science and Health: Possibilities, Probabilities, and Limitations," presents an optimistic* view of what the future of medical science promises us.

* OPTIMISTIC FOR WHO? SCIENTISTS? THE PUBLIC? PHYSICIANS?

The third section, "Case Histories," contains three papers, two of which recount the social histories of earlier plagues, the Black Death and syphilis, while the remaining paper, by Baruch Blumberg, tells the story of hepatitis B and the search for a preventive vaccine.

The three papers in the last section, "Moral Dilemmas," concern the thicket of moral problems raised by the presence of lethal, contagious diseases. What norms should govern our thinking about responsibility, culpability, legality, and confidentiality? What does society owe the victims? What are the responsibilities of the carrier population? How do we deal with the patient's right to privacy in the face of the physician's duty to warn and the public's right to know?

These papers at their best illustrate how much there is to be learned from a colloquy among scientists, social scientists, and philosophers, all of whom are concerned with common problems.

The original versions of these papers were presented at a *Social Research* conference held at the New School for Social Research in 1988 and the papers appeared in the Autumn 1988 issue of the journal. The conference was made possible by the generous support of the Rockefeller Foundation and the Edna McConnell Clark Foundation for which I am extremely grateful. The initial plans for this conference emerged at a planning meeting in the fall of 1986 attended by Gert H. Brieger, William H. Welch Professor of the History of Medicine, Johns Hopkins; John Hollander, poet and professor of English at Yale University; Shirley Lindenbaum, anthropologist and colleague at the Graduate Faculty of the New School; Dorothy Nelkin, professor, Program on Science, Technology and Society, Cornell University, currently Clare Boothe Luce Visiting Professor, Department of Sociology, New York University; Kenneth Prewitt, political scientist and vice president of the Rockefeller Foundation; Susan Sontag, novelist and critic; Paul Starr, sociologist and professor at Princeton University;

Jamie Walkup, editorial associate and co-organizer of the conference, and myself.

The idea for this project was first suggested by my cherished friend, John Hollander. My valued colleague, Jamie Walkup, collaborated with me in its development every step of the way. I am especially grateful to them both.

I. The Definition and Control of Disease—An Introduction

BY CHARLES E. ROSENBERG

AIDS has reminded us of some very old truths, truths most Americans had managed to forget during the past four decades. Epidemic infectious disease is not simply a historical phenomenon—or one limited like famine to the nonwhite in remote continents. By the end of the 1970s, most Americans had come to regard themselves as no longer at risk; infectious disease was almost by definition amenable to medical intervention. Not since the last severe polio threats more than a quarter century ago has the United States experienced the collective fear of epidemic disease.[1]

AIDS has helped us remember some other things as well. One is the way in which epidemic disease mobilizes widespread social response to the same stimulus; because AIDS was new to the 1980s that response was particularly intense and illuminating. Our reactions have underlined both our common humanity and America's cultural and institutional diversity. Epidemics serve as natural sampling devices, mirrors held up to society in which more general patterns of social values and attitudes appear in sharp relief. AIDS has demonstrated as well the way in which epidemics take place at a number of levels—biological event, social perception, collective response,

[1] Influenza does not seem to have the same ability to inspire widespread fear—in part because we have also forgotten the 1918 flu epidemic.

and, finally, the individual, the existential and moral. Yet these several aspects of an epidemic can be disaggregated only for the purpose of analysis, for they are intricately linked and constantly interactive. Each disease entity, as a social phenomenon, is a uniquely configured cluster of events and responses in both the biological and social spheres. AIDS reminds us not only of the multiple levels at which disease exists, but the urgent need to understand the interactions between these constituent aspects of the phenomenon we call an epidemic. The following papers focus differentially, in fact, on those levels, Lederberg emphasizing the biological, Foege organized public policy, Nelkin and Gilman the individual and attitudinal. Finally, AIDS has made it clear that we are not masters of life; there are limits built not only into humankind's genetic makeup but into our changing ecological relationship with the rest of the world and the multiplicity of organisms that inhabit it.

We tend to think of ills as either fundamentally biological and unambiguous in their medical identity (rooted in a well-understood biopathological mechanism) or as value-laden and problematic in their relationship to medical models and medical authority. AIDS occupies a position at both ends of that spectrum; it is an affect-laden occasion for the blaming of victims while, at the same time, it is the consequence of a particular and extraordinarily deadly biological mechanism.[2] This new pestilence can hardly be considered an arbitrary exercise in the labeling of deviance.

It is a plague in the classic sense, allied to such predecessors as bubonic plague, yellow fever, and cholera. Joshua Lederberg's essay construes AIDS as pathobiological process and humankind as animal, subject to the ultimately unpredictable vagaries of its physical and biological environment. By invoking the logically linked contributions of Darwin and

[2] I have discussed these issues in greater detail in "Disease and Social Order in America: Perceptions and Expectations," *Milbank Quarterly* 64, Suppl. 1 (1986): 34–55.

Pasteur, Lederberg seeks to place his argument in a cosmic framework, in which man's cognitive capacities are but one variable in a complex, ever-changing, and unpredictable universe. When he alludes to the microbiological events that have taken place in his laboratory test tube, Lederberg refers metaphorically to man's place on earth—our particular test tube,* in which human population has increased rapidly and perhaps ominously in the past century.

Dorothy Nelkin and Sander Gilman focus on a rather different level: the way in which men and women have tended to reduce their sense of vulnerability in times of plague by defining others as the ailment's appropriate and likely victims—creating reassuring frameworks in which to control and disarm otherwise disconcerting realities. Cultural values and social location have always provided the materials for self-serving constructions of epidemiological risk. The poor, the alien, the sinner have all served as convenient objects for such stigmatizing speculations.

William Foege's essay emphasizes a rather more public and institutionalized response to epidemic disease. Public health is a contested terrain in which objective data interact with such factors as the status of physicians and assumptions about state power. The relationship between knowledge and its application is always subject to negotiation; every historian of public health is well aware of this disconcerting reality. The brief history of AIDS has illustrated this truth with disheartening clarity.

But if AIDS illustrates timeless themes, it suggests some aspects of novelty as well. The pace of change in the late twentieth century is intense—as exemplified, for example, in the rapidity with which air travel helped spread the virus or the speed with which modern laboratories identified this new clinical entity and demonstrated its cause. Other institutions, too, have shaped perception and response in novel patterns. The state and its several agencies, for example, as well as print and electronic media have played significant roles in shaping

* EARTH—OUR PARTICULAR TEST TUBE

the response of a diverse and fragmented society. We have available to us an array of policy and attitudinal choices vastly different from those available to Europeans when they encountered plague in the fourteenth century or cholera in the nineteenth.

But for many Americans the ultimate meaning of AIDS must be moral. The precise lesson to be drawn from the history of AIDS will differ, just as Americans differ among themselves in their religious and social orientations. I was particularly struck in this connection with the resonant image of Joshua Lederberg's test tube. The ultimate moral implicit in this metaphor would have been clear enough to that dauntless Massachusetts pioneer in public health, Cotton Mather. We are all sinners in a test tube, he might have observed, in the hands of an awesome and possibly angry God whose acts transcend man's capacity for understanding.

MATHER – PURITAN CLERGYMAN, THEOLOGIAN, WRITER,
CARRIED OUT RESEARCH ON PLANT HYBRIDIZATION.
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Plagues: Perceptions of Risk and Social Responses

BY WILLIAM H. FOEGE

POLYBIUS taught us, over 2000 years ago, that the world is an organic whole,[1] where everything affects everything. Plagues demonstrate that truth—crossing cultures, crossing time, but also joining cultures and time inextricably, influencing the births and deaths of people, careers, and nations. Indeed, in a recently overworked phrase, "plagues bend history."

Perhaps rivaling the Black Death, which has received so much attention, was the pandemic of cholera which broke the boundaries of India in the early nineteenth century, moved across Russia by 1830, caused havoc at Mecca in 1831, moved across Europe in 1831 and 1832, arrived in the United States and went by canal boat to Albany and then to the Missouri River by 1833, where it became the determining factor for many wagon trains over the next years. In 1835, Marcus Whitman, the first medical missionary to the American west, made his initial journey to Oregon and was credited with saving a wagon train by stopping a cholera outbreak.[2] That epidemic allowed him to earn his reputation and start a career. Twelve years later, another epidemic, this one of measles, led

[1] Polybius, Bk. I, pp. 3–4 (ca. 150 B.C.).

[2] Bernard DeVoto, *Across the Wide Missouri* (Boston: Houghton Mifflin, 1947), p. 220.

to the Whitman Mission massacre, ending his career and the lives of the mission personnel.[3]

The Whitman Mission story becomes a paradigm for what has happened across cultures and nations. In the early eighteenth century, British troops began to receive variolation with smallpox virus, after Lady Montagu introduced the practice she had observed in Turkey, where her husband was ambassador.[4] Fifty years later, the battle of Quebec, where American troops outnumbered the British two to one, was lost by American troops when smallpox swept through their ranks but spared the British troops who had been variolated. (Some Canadians to this day worship smallpox as the deliverer from United States citizenship.)

In 1801, Thomas Jefferson acquired smallpox vaccine and personally administered it to his family and neighbors at Monticello. In 1804, he gave vaccine to Lewis and Clark, instructing them to administer it to Indians because of their high mortality rates due to smallpox. But it was too little and smallpox opened the west, decimating tribes and breaking their spirit. DeVoto writes about the 1837 outbreak, "All summer long not a single Indian came to Fort McKenzie. . . . Early in the fall Culbertson set out to . . . find out what was wrong. . . . Then at the Three Forks he found a village. No sound came from it as he approached, there were no horses or dogs, no children, no uproar. Presently they smelled the stench and then 'hundreds of decaying forms of human beings . . . lay scattered everywhere among the lodges.' "[5] On July 14 a young Mandan died of smallpox. Six months later only a hundred of the 1600 Mandans were still alive and no tribal organization could be maintained. There are no full-blooded Mandans today.

What lessons have we learned from this continuous flow of

[3] *Ibid.*, pp. 371–372.

[4] Donald R. Hopkins, *Princes and Peasants: Smallpox in History* (Chicago: University of Chicago Press, 1983), pp. 47–49.

[5] *Ibid.*, p. 291.

plague history? Are we truly better off because of what has happened upstream, or do the problems continue to change so dramatically that the lessons are only marginally beneficial? In this first session, we can only touch on some of the lessons of plague history. My attempts will be modest—to say something about:

(a) the definition of plagues
(b) the perception of risk
(c) responses

Definition

The definition of plague offered by the 1986 *Webster Medical Desk Dictionary*, describing plague as an epidemic disease causing a high rate of mortality, is inadequate for several reasons. Epidemiologists now commonly use the term *epidemic* to describe an unusual occurrence of a disease or condition. Thus, while a single case of smallpox would constitute an epidemic, the million cases of gonorrhea each year in the United States would be considered an endemic disease but not necessarily an epidemic.

Therefore, two problems with *Webster's* definition of the term are particularly significant. First, plagues do not have to be epidemic: a plague can be endemic, a constant presence. Second, mortality rates should not be the criterion for measurement. In describing one plague, the Old Testament notes the presence of fiery serpents, now known to be Dracunculiasis, or Guinea worm. This disease is associated with low mortality, yet anyone who has seen this ugly, debilitating scourge of poor areas knows it is a plague.

In fact, the definition of plague continues to change. We can all accept that smallpox, yellow fever, and cholera have been major plagues of history. But, in the last ten years, our society has legitimately expanded the definition of plague to recognize

a plague of ancient and major proportions—that is, violence. Historically, the two major causes of premature mortality have been infectious diseases and violence. The violence plague resisted the best efforts of science, religion, and law until very recently. To characterize it as a plague appears accurate.

Other, newer uses of the word *plague* involve chemicals. The agent need not be a microorganism but can be a chemical such as benzene or kepone, which can produce acute or chronic illness. Also, it is now common to speak of a lung-cancer plague, an outbreak or plague of strokes or coronary occlusion. Since the use of the word has enlarged, perhaps a better working definition would be "a disease or other condition causing high mortality *or* morbidity and often accompanied by social dislocation."

Perception of Risk

The response to a plague or threat of a plague is in some ways dependent on the perception of risk held by individuals and decision-makers. The perception can be quite different for the same disease depending on whether it is endemic or epidemic. For example, twenty-five years ago, in the state of Bihar, India, smallpox was endemic. Year in and year out it caused devastating illness and a large number of deaths. It was a scourge to be feared, but it did not cause panic primarily because explanations for the disease were incorporated into the culture and this provided acceptance and perhaps even a fatalistic attitude. At the same time, in Africa, smallpox would infect a given geographic area only periodically. Writings of anthropologists indicate that in some cases this would result in panic, the flight of a village population, and extensive social disruption.

We know from recent studies that the perception of risk that people have for many conditions is unrealistic, unstable, and

influenced by illusions of control. For example, people have some concept that microorganisms entail different risks, and the fear of the AIDS virus is totally different from the fear of strep throat. But at the same time we bring far less discrimination to chemical risks. For many, chemical risks are blurred, with saccharin, nitrites, and cigarettes having similar risks.

These studies have also found that the amount of control felt by a person greatly changes the perception of risk. People will accept high risks with cigarette smoking, fast driving, drug use, and other similar activities if they have control of placing themselves at risk. But they will reject even small or nonexistent risks, such as with food additives, fluoridation, or radiation if they feel they have no control over the exposure.

This has undoubtedly been a factor in the perception of and response to plagues in the past. People who thought they had some control over their own destinies reacted in different ways. This could have played a role in the continuing flow of Europeans to West Africa in the nineteenth century, despite known endemic plague conditions such as yellow fever and malaria that exacted major tolls. We know that mortality rates were very high for early Europeans in West Africa. Mungo Park, a physician, led an expedition attempting to map the Niger River. Within a few months all but six of his men had died of disease. The last six drowned when their boat capsized.

As we learn from *Ladder of Bones,* missionaries may have felt a divine calling, but early traders accepted such plague risks because of the money involved and the knowledge that if they survived for one year they would be placed in supervisory positions.[6] They must have felt a degree of control which led them to the conviction that they were survivors.

The same phenomenon was operating when the early mountain men of 160 years ago went west. Their annual rendezvous made it clear that in some years over 50 percent of

[6] Ellen Thorp, *Ladder of Bones* (Great Britain: Fontana Books, 1966).

* SMOKING / DRUG USE ALSO PROMOTED IN MASS CULTURE

the newcomers died, and yet their belief that they were in control caused them to accept such risks.

The same phenomenon occurs with modern plagues. A recent article by Ken Warner gives the Las Vegas odds for smokers. The net effect of freeing our society from all tobacco mortality would be a life-expectancy increase of one to two years. The average gain for smokers would be four to five years. But not all smokers die because of tobacco, and therefore for the smoker who actually experiences a tobacco-related death the loss is approximately fifteen years.[7] Subjecting oneself to such a plague requires either a strong feeling of control that will allow one to beat the odds or a strong sense of fatalism with no ability to alter the future.

The same is seen with AIDS, where some feel no threat even in the face of high-risk behavior while others feel no control even in the absence of risk. Episodes such as we have seen in Arcadia, Florida, result from many converging vectors, including feelings of vulnerability, no control, scientific illiteracy in interpreting the data, and lack of confidence in the authorities who indicated that these children did not present a risk.

Response

A watershed event in plague history was the point when individuals or groups moved from fatalistic acceptance to nonfatalistic action. Whether that action was effective is a separate question, but action is an old response in most cultures. In West Africa, fetishers intervened on behalf of smallpox victims. They would explain to smallpox victims what they must do to appease the gods. If the patient lived, the fetisher could take the credit and receive the appropriate

[7] Kenneth E. Warner, "Health and Economic Implications of a Tobacco-free Society," *Journal of the American Medical Association* 258 (1987): 2080.

rewards. If the patient died, the fetisher would explain how the patient had failed to carry out the recommended actions.

From Africa to India, to the Soviet Union, to Western Europe, religious ceremonies, beliefs, and activities developed to intervene, to appease the smallpox deity in order to reduce the intensity of this plague. The use of the color red, for example, in fighting smallpox seems to have been common and practiced in diverse parts of the world. Whether there was a common origin to this practice that spread through trade and travel or whether it has a multifocal origin is unknown. Even in modern times, we still engage in symbolism in our desire to appease the deities, whether keeping innocent and harmless children with positive HIV tests out of school or staying out of drafts to avoid the cold virus.

Social Regression. Today, we have experts to comment on the social implications of plague. But it is important to note that in general it has been easier for society to get answers in the area of biology and chemistry than in the areas of sociology, law, and ethics. We have, for instance, found it less difficult to develop a test for HIV antibodies than to develop guidelines on how to use that test. Likewise it is easier to develop vaccines than to get societies to use them. The stress of a plague compounds the problem, and social regression has been a common effect of disease outbreaks in the past. From the mistreatment of individuals to the total breakdown of social interactions, disease outbreaks have distorted society.

This unfortunate trend continues with AIDS. At the individual level, old and new prejudices have surfaced. Most gay men would happily return to the social acceptance of 1980 rather than face the ostracism that the AIDS crisis has produced in the last three years. Haitians have had difficulty in securing jobs, and some countries require testing of foreign students. Tourism in Africa has been adversely affected, and while the lesson that we are citizens of one globe should be the predominant one to arise from this pandemic, instead AIDS is

causing social fragmentation throughout many cultures. A recent editorial in *Science* said, "We have our problems today but at least we are not burning witches to stop the spread of disease."[8] Perhaps, but our actions are just as primitive.

Effective Intervention. Contrary to what we might expect, effective intervention is not all recent and often cannot be attributed to a single social group, much less an individual. The isolation or quarantine of smallpox cases to prevent spread was practiced long before quarantine procedures were used by governments. In West Africa, villagers would build a hut outside of the village for the isolation of smallpox cases. Food and care would be entrusted to a person who had already recovered from the disease.

Variolation, or the use of smallpox virus (not cowpox or vaccinia virus), was developed as a successful intervention tool thousands of years ago in China, India, and Africa. It was an effective, empirically developed intervention that was eventually used throughout the world.

But it was Edward Jenner who, 192 years ago, changed the history of intervention by developing a plague-prevention tool that involved small risk, was easy to use, and was very effective. Poets had noted the nice complexions of milkmaids, but it required Jenner to ask the scientific questions whether that was true and, if so, why? This line of questioning led him to develop smallpox vaccine. Despite its many advantages, however, it took the world 181 years to fully capitalize on this development. The fact that we have gone over ten years without a case of smallpox should embolden us to vigorously attack other plagues.

Lessons in application have multiplied dramatically since that time. Semmelweiss taught us the importance of observation and careful analysis of the facts about disease transmission. He carefully noted the disparity between maternal

[8] Daniel E. Koshland, Jr., "The Epidemiology Issue," *Science*, Nov. 21, 1986.

mortality rates on one ward versus another and concluded that the doctors themselves were responsible by examining women after they were involved in performing autopsies. His solution, washing of hands between the two activities, is a monument to simplicity. As Emerson observed, one should avoid over-analysis since often the causes are quite superficial. John Snow also used observation as a tool in the 1850s, and his analysis led him to reach new conclusions about the transmission of cholera, conclusions that were used within decades around the world.

But perhaps the most important step in the response to plagues has not been the dramatic interventions of Semmelweiss, Snow, and others, but rather the much more mundane development of successful delivery systems. The "institutionalizing" of response techniques so that they are available to everyone and for every plague is a very recent innovation in the history of plague study and control. While the philosophical basis for public health is social justice, the scientific foundation for public health is epidemiology. Although epidemiology was not institutionalized as an academic subject until almost seven decades ago, when Wade Hampton Frost was detailed from the U.S. Public Health Service to establish a department of epidemiology at Johns Hopkins, it is now one of the foundation stones of every school of public health.

But it was not until 1949 that epidemiology became institutionalized in the practice of public health. In that year, Alex Langmuir went from Johns Hopkins to the Communicable Disease Center in Atlanta (thereby returning the loan the Public Health Service had made in the form of Wade Hampton Frost) and established the Epidemic Intelligence Service. The techniques he established are now used as standards, not only in the United States but throughout the world.

Langmuir also developed practical systems of surveillance—fundamental for epidemiological analysis—to collect on a routine basis the needed numerators and denominators.

Surprisingly, this country had no nationwide surveillance system for any disease until 1950. In that year a malaria-surveillance program was started, only to find that malaria had quietly disappeared from the country in the 1940s. The next national surveillance program was started for polio during the crisis of the Cutter vaccine incident of 1955. Now there are literally dozens of such systems.

A second important component of the surveillance system is the ability to analyze the information collected in order to define the outbreak or situation and to characterize the extent of disease, the determinants, and the effects. It was such routine analysis that characterized the early days of the AIDS epidemic, and epidemiological analysis predicted the impending problems with blood products. Reviewing the 1983 recommendations on AIDS control, it is evident that the major facts were clearly apparent, because of epidemiology, before a virus was ever isolated. Those 1983 recommendations identified the means of sexual and blood-product transmission and what could be done to prevent transmission.

A third component of the system is the reporting of information back to health departments, other government agencies, academic facilities, and to the public on a weekly basis, which allows everyone to make their own interpretations if they wish. In order to effect the necessary changes in behavior, the public must be able to trust health leadership and must be provided with the most complete and factual information possible. But are there exceptions to sharing information? Obviously, one should not needlessly hurt people, and it should be apparent that the usual medical confidentiality and respect for an individual's privacy are required if we are to retain the cooperation of the public in outbreak investigations.

Such collection, analysis, and response is not new. It is the essence of the examples given earlier with Snow and others. Indeed, even the Whitman massacre was due to the logical collection of data, the correct interpretation that the measles

outbreak being experienced by the Indians was due to the Whitman Mission attracting visitors, and the apparently logical intervention of getting rid of the mission.

What is new about the surveillance techniques established by Alex Langmuir is that they were set up to provide *ongoing* evaluations of disease conditions and systematic responses. In the 1960s and 1970s, the same systematic approaches were used around the world for smallpox, and consequently surveillance and epidemiology have become effective tools in most countries.

While we have had an accumulated benefit from all of the various discoveries, the most important lesson of plague history is the value of systematizing our generic approaches to disease control. Second, the lessons of plague history include the need for a surveillance system to accurately define the outbreak, its determinants, distribution, and effects. Third, constant and competent analysis is required to determine the vulnerable points and to develop appropriate interventions. Fourth, responses require providing information to all who need to know, including the general public, and the initiation of public and private control activities.

In conclusion, as bad as the AIDS epidemic is, think what it would have been like fifty or even a hundred years ago, before we had a national surveillance system, before we had the massive educational possibilities of television, before we had the technology for testing to protect the supply of blood products, and before we had a global health leadership in the form of the World Health Organization. 1991

We can take comfort from the lessons learned and at the same time recognize we haven't moved forward adequately in all areas. For example, last year for the first time in thirty-nine years, the United States defaulted on its payment to the World Health Organization, thereby weakening the global effort to control disease. This was not a scientific failure; it was a leadership failure. And it will come back to haunt us.

For all of our scientific advances, we will continue to face

plagues forever, and we must now put as much attention on developing our social, legal, and ethical capacities as we have our technical and scientific capacities. To invoke the words of Sir William Osler,* "Our mission is of the highest and the noblest kind, not alone in curing disease but in educating the people in the laws of health and in preventing the spread of plagues and pestilence." That is our goal.

* OSLER MADE CONTROVERSIAL REMARKS ON IMMIGRATION AND LATIN AMERICANS IN PARTICULAR. (WRITTEN UNDER THE PSEUDONYM "EGERTON YORICK DAVIS")

Pandemic as a Natural Evolutionary Phenomenon

BY JOSHUA LEDERBERG

My main thesis is that the progress of medical science during the last century has obscured the human species' continued vulnerability to large-scale infection. We fail to acknowledge our relationship to microbes as a *continued* evolutionary process. This is far from equilibrium, and we cannot take for granted near-term outcomes that would be optimal from either our, or our parasites', perspective. We have a reasonable lead on bacterial intruders; we grossly neglect the protozoan parasites that mainly afflict the third world; we are dangerously ignorant about how to cope with viruses.

Pasteur and Darwin

Charles Darwin's role in nineteenth-century thought, how that shapes our own thinking about man's place in Nature, is too well known and oft discussed to bear extensive elaboration on my part. His contemporary, Louis Pasteur, is a culture hero, world renowned for the human benefits of his germ theory of disease: the use of antiseptic hygiene and of vaccines to prevent infection.

The ideological interaction of these two iconoclasts has been given too little attention. In his correspondence, Darwin makes enthusiastic but passing reference to Pasteur's humanitarian

contributions.[1] Pasteur's correspondence has been less extensively indexed to date.[2] The most notable allusion to Darwin in his published work is his address to the Sorbonne on April 7, 1864: "Great problems are in question today, which keep all spirits in suspense: . . . the creation of man several thousand years or several thousand centuries ago; the fixity of species, . . . the idea of a useless God." There is little doubt he is referring to Charles Darwin, whose work had been translated into French in 1862 and promptly aroused a theological storm. Pasteur is determined, however, to remove himself from that debate and such mysteries. Instead, he insists on addressing only those questions accessible to experiment, namely, the contemporary claims of spontaneous generation of microbial life. In 1864, his refutation was in comfortable support of an orthodoxy that would invoke the Creator for the ultimate origin of life. Indirectly, it was an argument against a Darwinian evolution of life arising in "some warm little pond."[3] Pasteur did show that the plethora of empirical claims of abiogenesis in sterilized broths exposed to air could all be accounted for by airborne spread of existing germs. By 1883, he had returned more optimistically to mechanistic views of abiogenesis if only one could achieve biochemical asymmetries, perhaps by the use of electromagnetism. Nevertheless, there is no record that he ever achieved a sympathetic understanding of Darwinian evolutionary theory; and he seems always to have been hostile to a methodology of inference, like Darwin's, that deviated from the grain of laboratory experiment.[4]

[1] Darwin to Bentham, 1863; Darwin to Romanes, 1875.

[2] Pasteur's correspondence is being opened to scholars at the archives of L'Institut Pasteur, Paris.

[3] Charles Darwin to J. D. Hooker (1871). "It is often said that all the conditions for the first production of a living organism are now present, which could ever have been present. But if (and oh! what a big if!) we could conceive in some warm little pond, with all sorts of ammonia and phosphoric salts, light, heat, electricity, &c., present, that a protein compound was chemically formed ready to undergo still more complex changes, at the present day such matter would be instantly devoured or absorbed, which would not have been the case before living creatures were formed."

[4] John Farley, "The Social, Political, and Religious Background to the Work of Louis Pasteur," *Annual Review of Microbiology* 32 (1978): 133–154.

On Darwin's side, for all his appreciation of Pasteur's medical contributions, he seems never to have incorporated microbiology into his natural history. And, as we know, neither of them had any inkling of two other contemporaries' contribution to fundamental biological understanding. Gregor Mendel's foundations of genetics, articulated in 1865, were buried until 1900. Friedrich Miescher had discovered nucleic acids (DNA) in pus cells in 1870; we were not to begin to understand the biological function of DNA until Avery, MacLeod, and McCarty's work at the Rockefeller Institute in 1944.[5] The latency of DNA research may be ascribed mainly to deficiencies in experimental technique whose repair needed decades of drudgery and many instrumental inventions. The barriers among Darwin, Pasteur, and Mendel were purely cerebral and ideological.

What lost opportunity! Darwin might have found, as present-day investigators do, marvelous experimental material for the study of evolution in populations of microbes—where generation time is measured in minutes, and where natural (or artificial) selection can be applied to tens or hundreds of billions of unicellular organisms at small cost and less ethical compunction. Pasteur and his successors in microbiology might have avoided decades of muddled thinking about variation in bacteria. The revolution in biotechnology could have had a couple of decades' head start. I should not complain: I had the fun and advantage in 1946 of exploring a terra still incognita (genetics of bacteria) that might otherwise have been blanketed with homestead claims for four or five prior decades.[6]

Plagues

Darwin had placed *Homo sapiens* at the pinnacle of the

[5] O. T. Avery, C. M. MacLeod, and M. McCarty, "Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types," *Journal of Experimental Medicine* 79 (1944): 137–518.

[6] H. A. Zuckerman and J. Lederberg, "Forty Years of Genetic Recombination in Bacteria: Postmature Scientific Discovery?," *Nature* 327 (1986): 629–631.

evolutionary process, but with as much emphasis on pinnacle as on evolution. He never quite rectified the view that man has a privileged place in nature. Man's intelligence, his culture, his technology has of course left all other plant and animal species out of the competition. Darwin was oblivious about microbes as our competitors of last resort. In experimental science, the Darwinian and Pasteurian perspectives are at last fully integrated. The study of mechanisms of virulence is a top priority in research laboratories applying the most advanced techniques of molecular genetics. Since Theobald Smith in 1934, F. M. Burnet and R. Dubos[7] have offered us broad perspectives of the natural history of infectious disease—perspectives that leave no illusions about the feasibility of eradicating our scourges, of the ongoing struggle. For a period, the works of Paul de Kruif dramatized the efforts of the "microbe-hunters."[8] But one legacy of the "miracle drugs," the antibiotics of the 1940s, has been an extraordinary complacency on the part of the broader culture. Most people today are grossly overoptimistic with respect to the means we have available to forfend global epidemics comparable to the Black Death of the fourteenth century (or, on a lesser scale, the influenza of 1918), which took a toll of millions of lives! We have no guarantee that the natural evolutionary competition of viruses with the human species will always find ourselves the winner.

I would ask the professional cultural historians for their comment; but it appears that our half-century has turned away from external nature and to the self-deprecation of human nature, or of human organizations, as the central target of fear and struggle. Not that we have to quarrel over pride of place between virus infection and nuclear doomsday.

[7] Theobald Smith, *Parasitism and Disease* (Princeton: Princeton University Press, 1934); F. M. Burnet and D. O. White, *Natural History of Infectious Disease* (Cambridge: Cambridge University Press, 1972); 1st ed. 1940); R. Dubos, *Man Adapting* (New Haven: Yale University Press, 1965). See also Hans Zinsser, *Rats, Lice and History* (Boston: Little Brown, 1935).

[8] Paul de Kruif, *Microbe Hunters* (New York: Harcourt Brace, 1926).

The countercultural protest against technology posits a benign nature, whose balance we now disturb with diabolical modernities. But man himself is a fairly recent emergent on the planet; the sheer growth of our species since the paleolithic is the major source of disturbances to that hypothetical balance. Man as a creature of culture is a man-made species; for better or worse, the only planet we know is a Promethean artifact. Genesis mandates: "Be fruitful and multiply!" After sampling the tree of knowledge, and acquiring the means, we could return to Eden only by reducing the human population to about 1 percent of its current density. We are complacent to trust that nature is benign; we are arrogant to assert that we have the means to except ourselves from the competition. But our principal competitors for dominion, outside our own species, are the microbes: the viruses, bacteria, and parasites. They remain an interminable threat to our survival.

This harsh view may be a product of my day-to-day laboratory experience. Most of my own scientific contributions have entailed the relentless use of artificial selection[9] as a way to detect rare differences in the genetic makeup of individuals in large populations. These were populations of bacteria; but they numbered in the billions in each test tube. Typically, all but a few of these would be wiped out by the chemical or virus intentionally added to remove that "normal background"; a few survivors of uncharacteristic genetic composition are then readily detected and isolated. So I have personally observed, even contrived, the wipeout of populations on a gigascale, and of course recognize that this is an unremitting process in nature—for example, recovery from infection on the part of any patient. This may come about either by the administration of an antibiotic or the mobilization of the naturally evolved defense mechanisms of the patient. In such confrontations, either the human individual or billions of microbes must die.

[9] J. Lederberg, "The Ontogeny of the Clonal Selection Theory of Antibody Formation: Reflections on Charles Darwin and Paul Ehrlich," *Annals N.Y. Acad. Sci.* 546 (1988): 175–187.

As Twort and d'Herelle first observed over seventy years ago, such competition can be seen within the microbial world, in nature or in the microcosms of the test tube: for bacteria have their own viruses, often in uneasy equilibrium with their hosts. It is not unusual to observe a thriving bacterial population of a billion cells undergo a dramatic wipeout, a massive lysis, a sudden clearing of the broth, in consequence of a spontaneous mutation extending the host range of a single virus particle. The bacteria will be succeeded by a hundred billion viruses—whose own fate is now problematical, as they will have exhausted their prey (within that test tube). There may, or may not, sometimes be a few bacterial survivors, mutant bacteria that now resist the mutant virus; if so these can repopulate the test tube—until perhaps a second round, a mutant-mutant virus appears.

Is there any reason to believe that such processes are unique to the test tube, that life in the large is exempt from them? Of course not! Only the time scale is certain to be different, by a factor of years to minutes, of a million to one, the disparity of generation time of human to bacteria. The fundamental biological principles are the same. The numerical odds may be different, by a factor hard to estimate.

As crowded as we are, humans are more dispersed over the planetary surface than are the "bugs" in a glass tube, and we have somewhat fewer opportunities to infect one another, jet airplanes notwithstanding. The culture medium in the test tube offers fewer chemical and physical barriers to virus transmission than the space between people—but you will understand why so many diseases are sexually transmitted. The ozone shield still lets through enough solar ultraviolet light to make aerosol transmission less hospitable; and most viruses are fairly vulnerable to desiccation in dry air. The unbroken skin is an excellent barrier to infection; the mucous membranes of the respiratory tract much less so. And we have evolved immune defenses, a wonderfully intricate machinery for producing a panoply of antibodies, each specifically attuned to the chemical makeup of a particular in-

vading parasite. In the normal, immune-competent individual, each incipient infection is a mortal race: between the penetration and proliferation of the virus within the body, and the development of antibodies that will dampen or extinguish the infection. If we have been vaccinated or infected before with a virus related to the current infection, we can mobilize an early immune response. But this in turn provides selective pressure on the virus populations, encouraging the emergence of antigenic variants. We see this most dramatically in the influenza pandemics; and every few years we need to disseminate fresh vaccines to cope with the current generation of the flu virus.[10]

Many quantitative mitigations of the pandemic viral threat are then inherent in our evolved biological capabilities of coping with these competitors. Mitigation is also built into the evolution of the virus: it is a pyrrhic victory for a virus to eradicate its host! This may have happened historically, but then both that vanquished host and the victorious parasite will have disappeared. Even the death of the single infected individual is relatively disadvantageous, in the long run, to the virus—compared to a sustained infection leaving a carrier free to spread the virus to as many contacts as possible. From the virus's perspective, its ideal would be a virtually symptomless infection, in which the host is quite oblivious of providing shelter and nourishment for the indefinite propagation of the virus's genes. Our own genome probably carries hundreds of thousands of such stowaways. The boundary between them and the "normal genome" is quite blurred; intrinsic to our own ancestry and nature are not only Adam and Eve, but any number of invisible germs that have crept into our chromosomes. Some confer incidental and mutual benefit. Others of these symbiotic viruses (or "plasmids"[11]) have reemerged as oncogenes, with the potential of mutating to a state that we

[10] E. D. Kilbourne, *Influenza* (New York: Plenum Medical, 1987).

[11] J. Lederberg, "Cell Genetics and Hereditary Symbiosis," *Physiology Review* 32 (1952): 403–430.

recognize as the dysregulated cell growth of a cancer. As much as 95 percent of our DNA may be "selfish," parasitic in origin.

At evolutionary equilibrium, we would continue to share the planet with our parasites, paying some tribute but deriving some protection from them against more violent aggression. Such an equilibrium is unlikely on terms we would voluntarily welcome: at the margin, the comfort and precariousness of life would be evenly shared. No theory lets us calculate the details; we can hardly be sure that such an equilibrium for earth even includes the human species. Many prophets have foreseen the contrary, given our propensity for technological sophistication harnessed to intraspecies competition.

In fact, innumerable perturbations remind us that we cannot rely on "equilibrium"—each individual death of an infected person is a counterexample. Our defense mechanisms do not always work; viruses are not always as benign as would be predicted to serve their long-term advantage.

The historic plagues, the Black Death of the fourteenth century, the recurrences of cholera, the 1918 swine influenza should be constant reminders of nature's sword over our head. They have been very much on my mind for the past two decades.[12] However, when I have voiced such fears, they have been mollified by the expectation that modern hygiene and medicine would contain any such outbreaks. There is, of course, much merit in those expectations: the plague bacillus is susceptible to antibiotics, and we understand its transmission by rat-borne fleas. Cholera can be treated fairly successfully with simple regimens like oral rehydration (salted water with a touch of sugar). Influenza in 1918 was undoubtedly complicated by bacterial infections that could now be treated with antibiotics; and if we can mobilize them in

[12] J. Lederberg, "Biological Warfare and the Extinction of Man," *Stanford M. D.* 8 (Fall 1969): 15–18; J. Lederberg, "Orthobiosis: The Perfection of Man," in Arne Tiselius and Sam Nilsson, eds., *The Place of Value in a World of Facts: Nobel Symposium XIV* (New York: John Wiley & Sons, 1970); J. Lederberg, "The Infamous Black Death May Return to Haunt Us," *Washington Post*, Aug. 31, 1968.

time, vaccines can help prevent the global spread of a new flu. On the other hand, the role of secondary bacterial infection in 1918 may well be overstated: it is entirely possible that the virus itself was extraordinarily lethal. The retrospective scoffing at the federal campaign against the swine flu of 1976 is a cheap shot on the part of critics who have no burden of responsibility for a wrong guess. It underrates health officials' legitimate anxiety that we might have been seeing a recurrence of 1918[13]—and underscores the political difficulty of undertaking the measures that might be needed in the face of a truly species-threatening pandemic. This so-called fiasco in fact mitigated an epidemic that happily proved to be of a less lethal virus strain. The few cases of side-effects attributed to the (polyvalent) vaccine are undoubtedly less than would have appeared from the flu infections avoided by the vaccination program. However, the incentives to attach fault for damages from a positive intervention have predictable consequences in litigation, not to be confused with the balance of social costs and benefits of the program as a whole.

Many outbreaks of viral or bacterial infections have destroyed large herds of animals, of various species, usually leaving a few immune survivors. With all the discussion of faunal extinctions, nothing has been said about infectious disease. It would be impossible to verify this from the fossil record, but disease is the most plausible mechanism of episodic shifts in populations. Incontrovertible examples of species wipeouts are seen with fungi in the plant world: Dutch elm disease and the American chestnut blight. Yes, it can happen.

My discussion has emphasized viruses because medical science has still to develop effective drugs for the treatment of virus infections—we have but a small handful, of limited use. Keep in mind that bacteria are free-living organisms whose metabolic peculiarities lend themselves to differential attack. For example, the bacterial cell wall is utterly unlike any

[13] Kilbourne, *Influenza*.

structure found in human cells. Hence, penicillin, which attacks the integrity of the bacterial cell wall, is all but innocuous to human tissue, and can be given in very large doses so as to saturate every susceptible bacterial cell. Viruses, on the other hand, are genetic fragments which live within the host cells and exploit their metabolism. It has so far been very difficult to find chemicals that will inhibit a virus without harming the host cell at the same time. Our principal strategy for dealing with viruses is immunization, evoking antibodies that recognize the peculiarities of the virus surface. When a virus, like AIDS, comes along and targets the immune system itself, we are left with dimmer hopes of being able to use that strategy; and we have very few alternatives.

Our main concern about bacterial plagues is for the emergence of antibiotic-resistant strains of familiar threats—for example, chloramphenicol-resistant typhoid. Plasmids are known to travel among bacterial strains and confer antibiotic resistance. Hence selective pressures favoring antibiotic-resistant mutations in the bacteria in cattle's intestines (by our routinely feeding them antibiotics) have ended up making it more difficult to treat human disease with the same drugs. Probably even more important, and more difficult to control, is the inappropriate use of antibiotics for trivial human disease, or often for viral infections which antibiotics cannot control anyhow, with the same result. In effect, any antibiotic will have a limited lifetime of practical use; but we have devised no way of rationing that to be sure it saves the most lives. (On the other hand, it has been surmised that the indiscriminate use of penicillin, by purely incidental effect, is the main cause for the drastic mitigation of syphilis in the United States, most cases having been treated unintentionally. Here we have been unaccountably lucky that penicillin-resistant syphilis just hasn't emerged. We don't know why.) We have been in a well-chronicled race: human wit in the development of new antibiotics versus the evolutionary drive for the emergence of resistant mutants. We gained an enormous lead during the

1940s' discoveries of these magic bullets; on the whole we probably have the appropriate incentives and scientific understanding to retain that lead, at least in the developed countries. As must be reiterated, our neglect of infectious disease in the poor majority of the world is not just a humanitarian disgrace; it leaves unchecked the seeds of our parochial infection.

Besides drug-resistance, bacteria do have some surprises for us: in recent history, the spreading tick-borne epidemic of Lyme arthritis and the storied Legionella show what can emerge overnight; and how perplexing that can be until the parasite is isolated and identified. Other mysterious variations in lethality of bacterial infections come to notice from time to time. Besides the fluctuations of environment that are usually invoked, closer attention should be given to the likelihood that the bacteria themselves may undergo genetic evolution. This may be alarming, insofar as we cannot be sure that the plague bacilli we see today, and believe we can control, are just the same as those responsible for the fourteenth-century pandemic.

Technology's impact is not all on the human side of the struggle. Monoculture of plants and animals has, of course, made them more exposed to devastation. In like fashion, the increasing density of human habitations, inventions like the subway and the jet airplane, all add to the risks of spread of infection. Paradoxically, improvements in sanitation and vaccination leave the larger human herd more innocent of microbial experience, and may in the long run make us the more vulnerable. On the other hand, the loosening of ethnic barriers has made the human population a mite more variable, and in principle better equipped to deal with biological challenges. Evolutionary modes of adaptation, we must never forget, carry a terrible cost in the lives of extant individuals. The best-known example in the human is the sickle cell trait, evolved in Africa as an adaptation to malarial infection. The ancestral benefit to the heterozygotes is exacting a cost today in sickle cell disease among the homozygotes, about two births

per thousand among American blacks. The evolutionary calculus tells us this will come to equilibrium only when as many homozygotes have died (or will not be born) as ancestral heterozygotes had been saved from malaria. Infectious disease has undoubtedly loomed large among the selective factors shaping the human genome, and eventually will help explain the polymorphisms in blood groups and in histocompatibility (tissue-graft) antigens. We have had plausible speculations that genetic diseases like the Tay-Sachs syndrome may have conferred some protection against tuberculosis.

Technology, manifest in the opening of wild lands to human occupation, has also exposed people to unaccustomed animal viruses, to zoonoses. Yellow fever has sustained reservoirs in jungle primates, and the same source is the probable origin of the HIV virus in Africa. It is mystifying that yellow fever has not become endemic in India, where competent mosquitoes and susceptible people abound. We will almost certainly be having like experiences from the "opening" of the Amazon basin.

More remote, perhaps more farfetched, is the interplanetary transfer of infection. My own concerns, since Sputnik,[14] have addressed the need to quarantine the planets, more to protect them from contamination from a germ-laden earth than vice versa. The main values at stake are in scientific understanding, which will certainly be confused should we find bacterial spores on Mars and have not undertaken hygienic precautions beforehand. So long as we do not rush people to Mars (which bears the concomitant imperative of returning them to earth), we can do all the necessary preliminary science with clean, unmanned missions, as has been internationally agreed policy to date.

AIDS and Other Plagues

The sudden and tragic spread of AIDS has brought us back

[14] J. Lederberg, "Sputnik 1957–1987," *Scientist*, Oct. 5, 1987.

to earth in our speculation on plagues: who among us has not been personally touched already! A host of social and ethical issues come right to home, and will be the main focus of this conference. As always, the third world is paying the heaviest price, in the dying of whole villages and in the stigma of the biological origins of the virus. We are all in fear of what will come next. Will the virus spread still further? What are the prospects of a vaccine? Of a cure?

You will have professional epidemiologists speak to the current statistics. There is nothing hopeful about them. But you should not think that AIDS is our only plague. In the third world, tuberculosis and malaria are until now just as devastating in their public-health impact, and are likely to remain deathly competitors to AIDS in toll on human life. Unlike AIDS, most of the third world endemics are most painful as chronic diseases, which kill millions to be sure but leave many more in debilitation and suffering, still-hungry mouths to be fed. On top of those, over 3 million children a year die of diarrheal disease, a like number from infections for which effective vaccines exist but have not been available where needed. This enormous mortality is entirely preventable. The neglect of it is related to the history of a new disease that must have been spreading unremarked in Africa for ten or fifteen years before it emerged in the Western Hemisphere. Nor will AIDS be the last example of its kind.

We are all too familiar with the factors that have made AIDS an especially ugly challenge. Unlike other virus infections, which leave some survivors immune to further attack, there is nothing in the natural history of AIDS to point either to a cure or to a vaccine. Victims develop antibodies, then go on notwithstanding to develop more aggravated disease, with the eventual collapse of the immune system. The fact that this is still mysterious makes it the most promising avenue for new discovery and possible intervention. Most of the factual knowledge we have is unremittingly discouraging.

The long latent period multiplies the opportunity for

spread; the victim may be unaware of carrying the virus, even less his contacts. Nothing could provoke more anxiety than this protracted uncertainty. The targeting of the immune system also encourages the seeding of other infections—we are already starting to see a recrudescence of tuberculosis in the United States and aggravations of syphilis and a host of opportunistic organisms rarely seen before. It would be far worse were HIV still more readily spread, but its substantial confinement to special high-risk groups worsens the social tensions around efforts at control. The long latent period guarantees a large number of momentarily healthy carriers whose civil rights—for example, to continued schooling and employment—are in instant conflict with a quarantine mentality for public-health control. I was labeled an alarmist twenty years ago for raising a "specter" of pandemic. My most pessimistic imagination did not fetch the constellation of attributes that we observe with AIDS. AIDS is already so prevalent in the United States today that none of the approaches of public-health control of other acute infections are pertinent. There is little merit in targeting a handful of individuals, generally the most compliant, when there are a score as many freely walking the streets.

So much is unknown about AIDS that a large amount of testing is essential just to understand the scope and localization of the problem. We may soon find that many hospital and medical procedures aggravate AIDS infection: that will obligate broader testing of AIDS among hospital admissions, simply for the patients' benefit. And they will sue for not having been routinely tested. Health-care personnel have an ethical obligation to care for all the sick; but this is complemented by a right to know what they need to protect their own health. We will not work out the most viable balance between individual rights and the community's needs without a great deal more compassionate thought and inevitable political stress. Both need to be informed by more reliable knowledge.

Will AIDS get even worse? It may already be worse than we

believe—there is a fair possibility that some potential carriers are still uncounted, that they will have a long latent period after primary infection, before the virus reemerges and before antibodies begin to appear. Such a stage at least is not fraught with transmitting the disease to others. We have yet to learn more precisely how readily it can be transmitted by heterosexual contact; there is not much point trying to predict the future course of AIDS prevalence by simple arithmetic extrapolation, when utterly different communities and vehicles are involved. We have Africa as a dismal historic example of progressively broad spread; and I am not much impressed by arguments that speak to cultural idiosyncrasies (as opposed to mere time) as the difference between their experience and ours. Regardless, with what we know we have on our hands, we have a rough road ahead.

As with some health-care workers, we are likely to experience a few cases of AIDS transmitted outside the "high-risk behaviors." As such, these will have a political impact far beyond their public-health importance, in contrast to the recognized, dominant modes of transmission. We have to be careful not to be stampeded by a few tragic accidents statistically equivalent to lightning bolts. Rarely in human history has so much rested on the clarity of social decision-making, subject to extraordinary constraints of group interest, prejudice, and ignorance.

Will AIDS mutate further? Already known, a vexing feature of AIDS is its antigenic variability, further complicating the task of developing a vaccine. So we know that HIV is still evolving. Its global spread has meant there is far more HIV on earth today than ever before in history. What are the odds of its learning the tricks of airborne transmission? The short answer is, "No one can be sure." But we could make the same attribution about any virus; alternatively the next influenza or chicken pox may mutate to an unprecedented lethality. As time passes, and HIV seems settled in a certain groove, that is momentary reassurance in itself. However, given its other ugly

attributes, it is hard to imagine a worse threat to humanity than an airborne variant of AIDS. No rule of nature contradicts such a possibility; the proliferation of AIDS cases with secondary pneumonia multiplies the odds of such a mutant, as an analogue to the emergence of pneumonic plague. Such cases warrant and receive close-isolation precautions; but who will ensure that in Africa? We must particularly look more deeply into the biological mechanisms that govern how AIDS can or cannot be transmitted; our current assessments are crude empiricisms. And with so much at stake we must multiply our vigilance for evidence of extraordinary channels of spread.

Our preoccupation with AIDS should not obscure the multiplicity of infectious diseases that threaten our future. It is none too soon to start a systematic watch for other new viruses before they become so irrevocably lodged. The fundamental bases of virus research can hardly be given too much encouragement—and they have made extraordinary leaps, particularly with the help of recombinant DNA technology.[15] Such research should be done on a broad international scale, both to share the progress made in advanced countries and to amplify the opportunities for fieldwork in the most afflicted ones.

We also have some political lessons learned. Hard-won human rights, the autonomy of individuals, will be in conflict with the quietude of the community. At severe cost, if at all, will it be possible to impose traditional disease-control methods like isolation and quarantine on new viruses? Compulsory

[15] The sensational publicity given ca. 1975 to the hypothetical hazards of recombinant DNA research ignited public fears and regulatory reactions that boded ill for the opportunity to continue research on methodology of the most crucial importance for the understanding of virus infection. Some participants at the much-heralded Asilomar Conference treated such research as if it were an idle diversion for the amusement of scientists; therefore what harm in an indefinite moratorium? See J. Lederberg, "DNA Research: Uncertain Peril and Certain Promise," in J.D. Watson and J. Tooze, *The DNA Story: A Documentary History of Gene Cloning* (San Francisco: Freeman, 1981).

vaccination has all but passed the pale. Claims for redress for individual harm from medical accidents from vaccines necessitate that we find new social-insurance approaches to indemnification. Failing that, we have already seen a collapse of the pharmaceutical industry's incentive and capability for pursuing new vaccine developments. The most stunning victories will be quiet ones, against viruses we have learned enough about beforehand to keep them from planting a foothold.

The stresses on democratic civility posed by AIDS have no precedent in U.S. history. They are compounded by our scientific uncertainties as to where this epidemic is heading. The best available advice is incorporated in the program advocated by the leadership of the federal health agencies and the expertise of groups like the National Academy of Sciences.[16] That advice can be no more authentic than the empirical findings to date. It is of the greatest urgency that these be bolstered by a more robust appreciation of virus biology and of the human immune mechanism. At present, nothing we know gives us assurance of finding satisfactory cures or vaccines for AIDS infection. We can take small comfort that much more remains to be explored—but only if we mount that exploration with the most urgent priority.

Additional Comments

P. 28. The general theme that virus-host relationships evolve towards less virulent, stable commensalism has been criticized by R. M. May and R. M. Anderson. "Parasite—host coevolution." *Parasitology* 100: S89–S101, 1990. They stress that selection within the infected host favors the more virulent geno-

[16] Institute of Medicine, National Academy of Sciences, *Confronting AIDS: Directions for Public Health, Health Care, and Research* (Washington, 1986). Regarding AIDS see more recently: Eve K. Nichols, *Mobilizing Against AIDS* (Washington: National Academy of Sciences, 1989); H. Mitsuya, R. Yarchoan, and S. Broder, "Molecular Targets for AIDS Therapy," *Science* 249 (1990): 1533–1544; A. S. Fauci, "The Human Immunodeficiency Virus—Infectivity and Mechanisms of Pathogenesis," *Science* 239 (1988): 617–622; Hung Fan et al., *The Biology of AIDS* (Boston: Jones & Bartlett, 1989).

types, however this may result in a deprivation of prey for further spread of the parasite. Nevertheless, many stable commensalisms and mutualistic symbioses have indeed evolved, culminating in the incorporation of mitochondria and chloroplasts as essential constituents of animal and plant cells. Cf. L. Margulis, *Symbiosis in Cell Evolution.* San Francisco: Freeman, 1982.

P. 32. For further detail on looming threats from new and emerging viruses, see Stephen Morse, ed., *Emerging Viruses.* Princeton: Princeton University Press, to be published in 1991.

P. 35. Three years' further experience has fortunately given no direct evidence of more facile spread of HIV, e.g., by airborne transmission. We have only the general comfort that HIV "is not very infectious" as theoretical grounding for this observation, and continued vigilance remains warranted. Antigenic variability of HIV does appear to be a complication for efforts to develop a vaccine. T. F. W. Wolfs, et al. "Evolution of Sequences Encoding the Principal Neutralization Epitope of Human Immuno-deficiency Virus 1 Is Host Dependent, Rapid, and Continuous." *Proc. Nat. Acad. Sci. U.S.* 87 (1990): 9938–9942.

Addendum to Footnotes

1. C. Darwin to G. Bentham, May 22, 1863. Darwin to F. Holmgren, April 14, 1881. Darwin to F. J. Cohn, January 3, 1878: The calendar to Darwin's correspondence, on the other hand, records several letters from medical people inquiring about the correlation of evolutionary principles to infection, but with no reply indicated. See F. Burkhardt and S. Smith, eds., *A Calendar of the Correspondence of Charles Darwin, 1821–1882. (New York: Garland, 1985).*

3. The calendar (v.s.{1}) remarks that Pasteur's experiment on abiogenesis is mentioned in this letter, which has not been published in full text to date.